

VU Research Portal

Prevention of Depression in later life. A developmental perspective

Beekman, A.T.F.; Cuijpers, P.; Smit, H.F.E.

published in

Late life mood disorders.

2013

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Beekman, A. T. F., Cuijpers, P., & Smit, H. F. E. (2013). Prevention of Depression in later life. A developmental perspective. In H. Lavretsky, M. Sajatovic, & C. F. Reynolds (Eds.), *Late life mood disorders*. (pp. 448-456). Oxford University press.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

25

PREVENTION OF DEPRESSION IN LATER LIFE

A DEVELOPMENTAL PERSPECTIVE

Aartjan T. F. Beekman, Pim Cuijpers, and Filip Smit

In: Lavretsky H, Sajatovic M, Reynolds CF (Eds).
Late life mood disorders. Oxford University
Press, 2013

THROUGHOUT HEALTH care, everything we do is aimed toward prevention. This ranges from preventing the onset of disease in those who are well, through preventing chronicity, disability, and other consequences of disease in those who are ill, to preventing relapses in those who have recovered. Mrazek and Haggerty (1994) have defined and delineated the various types of prevention that are involved in different phases of development of disease. Inspired by their pioneering work, Figure 25.1 brings together a schematized developmental history of disease and the corresponding types of preventative action that would be appropriate in each stage (Beekman, 2004).

Universal prevention targets the whole population and aims to help reinforce resilience or prevent health risks. Selective prevention is restricted to those who are exposed to known risk factors for disease. The aim is to prevent the onset of disease efficiently, by focusing on those who are known to be at high risk. Depending on how common the risk factor is, this involves far fewer people than the whole population. However, depending on how easy it is to

screen out those who are exposed to a risk factor, this involves more or less cumbersome and expensive screening procedures. Indicated prevention is aimed at people who exhibit some signs or symptoms of the disorder but in whom there is no fully developed disease as yet. The terminology used to describe the symptoms of those involved in indicated prevention varies from subclinical or subthreshold symptoms, to prodromal symptoms. The people involved are on the brink of developing a full-blown disease and may be deemed at ultra-high risk or even in the early stages of the disorder. In terms of the number of people involved, this again involves far fewer people than the stage before (selective prevention), but again it may involve cumbersome or expensive screening procedures. Universal, selective, and indicated prevention share their aim of preventing the onset of full-fledged disease and are sometimes collectively named primary prevention. This chapter will focus on primary prevention of late-life depression, recognizing that it is part of a larger repertoire of interventions.

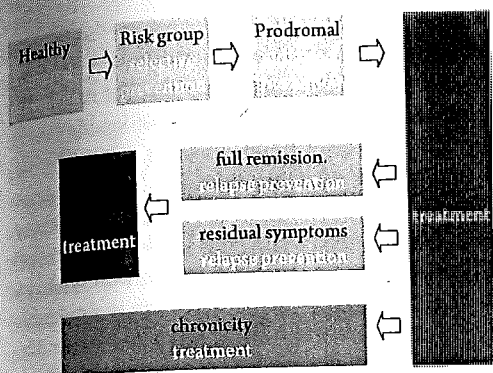


FIGURE 25.1 Developmental stages of mental disorder and corresponding preventive interventions (Beekman, 2004).

Prevention aims to interfere with the natural history or development of disease. In other areas of medicine the developmental history of disease is the starting point of diagnosis and treatment. In oncology, decades of clinical and scientific work have brought about a well-developed staging model of cancer (see Dighe et al., 2010; Hariharan et al., 2010; Paesmans et al., 2010; Xing et al., 2011 for some recent examples). The bottom-line idea behind this has been that early detection and treatment is the only way to prevent the disease from developing beyond the point at which treatment may be helpful. In most cancers there is a window of opportunity for treatments that work very well in patients who are detected early, but which lose their effectiveness later in the development of the cancer. Although this has not been proven in psychiatry, it is extremely likely that a similar line of reasoning would apply to most psychiatric disorders. Using this line of thinking, McGorry (2007) has convincingly argued for a staging approach to psychosis. The idea here is, similar to what has been achieved in oncology, to detect and treat psychosis as early as possible, hopefully thereby reducing the damage to both the patient and the community. The idea of staging psychiatric illness with the aim to prevent damage to the patient and to society is slowly finding its way in our field and has inspired the writing of the current chapter. Although staging is not yet well developed in psychiatric disorders, the models proposed have consistently included the stages summarized in Figure 25.1 (Fava & Kelner, 1993). As was described, these stages map onto different types of preventive intervention.

The next paragraphs will discuss (1) a staging and profiling model of late-life depression, (2) the corresponding types of preventative intervention that would be appropriate in the early stages of development of late-life depression, (3) the evidence of studies that have tested the effectiveness of such preventative interventions for late-life depression, and (4) the public health, economic, and ethical implications this may have.

STAGING AND PROFILING LATE-LIFE DEPRESSION

The dominant diagnostic guidelines in psychiatry (ICD and DSM) were designed with the principal aim to provide a universal language to reliably describe and classify psychopathology. Although successful, the resulting diagnoses are insufficiently sensitive to the stage of development, the etiology, or the prognosis of psychiatric disorders and are not sufficiently helpful in selecting appropriate treatment. Depression is a prime example of this.

Figure 25.2 summarizes prospective data of a large cohort of adult patients with major depressive disorder (MDD). The people under study were derived from a representative community survey in the Netherlands and were selected to include only recent-onset episodes of DSM-IV MDD (Spijker et al., 2003). The survival curve steeply declines over the first months, demonstrating that many patients

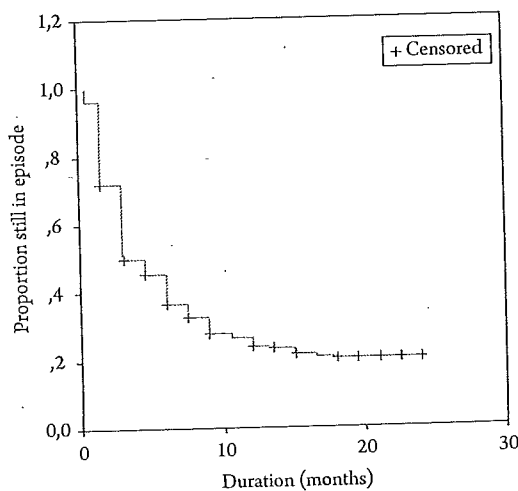


FIGURE 25.2 Survival curve of a cohort ($n = 250$) with newly originated (first or recurrent) major depressive episodes in the general population; +, censored cases (Spijker et al., 2003).

recover quickly. In more exact numbers, the median time to recovery was 3 months. Mostly this occurred without treatment. This would suggest that MDD, in many patients, is a self-limiting condition. However, the survival curve flattens out after the first 6–9 months. After the first year, very few people recover. When expressed in numbers, 20% of those diagnosed at baseline had not recovered after 1 year and were unlikely to recover any time soon after that. Evidently, the same diagnosis (MDD) may be indicative of both a self-limiting disorder and a chronic disease. For both clinical and research purposes, a diagnosis that is more sensitive to the prognosis would be desirable. A first step would be to adopt a simple staging model for depression, such as has been proposed for other psychiatric disorders (Fava, 1993; Hetrick et al., 2008).

Figure 25.3 also summarizes prospective data of a large cohort of patients diagnosed with MDD. These data were derived from a study among older (65+) patients of general practitioners in the Netherlands, who were recruited through screening (Licht-Strunk et al., 2009). Comparing the survival curves, it is striking that the prognosis is worse. The median time to recovery was 18 months, which is six times as long as what was found among the younger adults in the community. After 1 year, only 35% of the patients had recovered, compared with 80% in the younger community sample. However, after this first year the curve did not flatten out and people kept recovering. After 3 years, 68% had recovered and at the end of the study most patients had reached recovery. This suggests that the outcome may be similar in the long run, but that it takes a lot longer for older people to recover than it takes among younger people. A direct

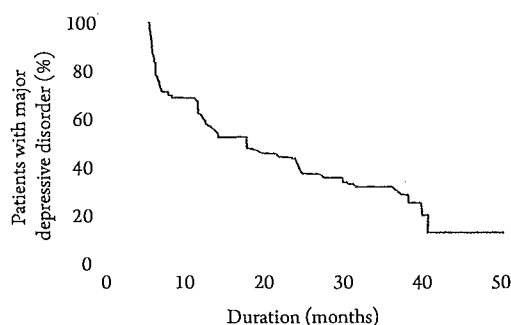


FIGURE 25.3 Survival curve of a cohort ($n = 204$) of older patients with major depressive disorder recruited from general practitioners' practices in the Netherlands (Licht-Strunk et al., 2009).

comparison is unfair because of methodological differences between the two studies involved, but the two sets of data do suggest that the natural history of depression may differ considerably by age. Is this plausible? Are there reasons one might have predicted this, or, better, are there factors that may explain this? Probably yes. Looking at the known risk factors to develop depression, later life presents people with a very different set of potential risks than earlier in life. This involves both the more biological domains of risk (such as neurodegeneration, cardiovascular and cerebrovascular risk, HPA-axis changes, and inflammatory markers), the interpersonal domain (loss of loved ones and loss of functioning and roles), and psychological changes (less cognitive and emotional reserve capacity). Indeed, among older people several "new" subtypes of depression have been described, which are deemed to be especially common in later life. Examples are vascular depression (Alexopoulos et al., 1997), metabolic depression (Lamers et al., 2010; Vogelzangs et al., 2011), and amyloid associated depression (Sun et al., 2008). In all the papers describing these putative subtypes of depression, reference is made to the idea that their prognosis would be different (usually worse) and that treatment would be different (usually directed not only at the depressive symptom but also involving the underlying etiology).

It appears that both the etiology and the prognosis of depression may differ for older when compared to younger adults and that this may be explained by the biological and psychosocial changes accompanying aging. This is described here for two reasons. The first is that a simple staging model of depression becomes much more informative when it is supplemented with data on factors that may predict whether transitions between the stages are more or less likely. This is what is meant with the word profiling: a profile of risk factors that predict transitions. The second point is that depression is a complex disorder at any age, but that this complexity increases in later life. A staging and profiling model for affective disorders would be especially helpful for geriatric psychiatry. Conversely, the development of such a model may benefit especially from research carried out among older patients.

PREVENTATIVE INTERVENTION

A critique of prevention in mental health would focus on (1) feasibility, (2) effectiveness, and (3) ethical and economic considerations. Effectiveness

is extremely next paragraph interventions would among older care in such a both ethical venting depression activity of it beyond heal because the proportionality intervention risk avoided

Universal

Universal prevention the whole population risk of depression majority of Therefore, a life depression terms of cost is a public launched in (2003) has depression, testing the intervention are unbiological common many participants current met universal prevention suggest that as a primer intervention is a diagnosis. Given the widespread acceptance health promoting for old shift prevention. With regard inclusion so preventive but that curious testing

Selective

Selective prevention are exposed a priori risk

methodological involved, but the natural history of depression is probably by age. One might have risk factors that may be at the known level of life presents potential risks for the more biodegeneration, risk, HPA-axis, the interper- loss of func- changes (less city). Indeed, subtypes of depression are deemed. Examples are (Sun, 1997), met- Vogelzangs et al., 1997), depression (Sun, 1997). These put- as made to the different (usu- symptom but the prognosis compared to the accompanying symptoms. The first symptom becomes prominent with the transitions. This is what the point of risk factor is that age, but that staging and could be espe- conversely, the fit especially atients.

ION

health would less, and (3) effectiveness

is extremely important and will be described in the next paragraph. Here we focus on what sort of interventions would be appropriate to prevent depression among older adults; how we should organize health care in such a way that this may be feasible; and, given both ethical and economic constraints, whether preventing depression is indeed a core business-type activity of mental health care or whether this goes beyond health care. The third point is discussed last because the answer to this question involves proportionality: The cost and impact of a preventative intervention should be proportional to the health risk avoided by those participating.

Universal Prevention

Universal prevention of late-life depression targets the whole population of older people. Although the risk of depression is considerable at all ages, the vast majority of older people will never be depressed. Therefore, any universal preventative action for late-life depression should be a light intervention: both in terms of cost and in terms of impact. A good example is a public awareness campaign, such as has been launched in many countries in the world. Cuijpers (2003) has described that, even in a disorder like depression, which has quite a high incidence, studies testing the effects of universal prevention in depression are unlikely to be feasible. Among other methodological constraints, such a study would require too many participants and be too costly to be run, given current methods of research. This does not imply that universal prevention may not be useful, but it does suggest that universal prevention is probably best seen as a primer—a way to prepare the public that depression is a disorder that one can do something about. Given the rapid technological advances and the widespread access to electronic media among older people, e-health preventative interventions especially catering for older people are being developed. This may shift preventative action toward universal prevention. With regard to feasibility and effectiveness the conclusion so far is that it is feasible to launch universal preventive programs aiming to prevent depression, but that current methods of research do not allow rigorous testing of their effects.

Selective Prevention

Selective prevention aims to reach older people who are exposed to known risk factors for depression. Their a priori risk to become depressed is elevated, tipping

the balance of proportionality more toward intervention. Examples are older people with chronic disease, those who have lost their spouse, and those who have been depressed before. If, through education, the public knows that these are risk factors for depression, and that it is a good idea to invest in prevention, selective prevention may become more mainstream.

Several tested interventions are available. They usually involve (1) a way of identifying and engaging those at risk and (2) the intervention proper. Identification of older people at risk and engaging them effectively depends very much on local factors. In high-resource countries with well-developed health services, the optimal point of contact for selective prevention may be the health service. In the Netherlands there are (as yet) very few financial barriers to health care. All citizens have compulsory health insurance and there is almost universal coverage by general practitioners (GPs). Epidemiological data have shown that the vast majority of older people with known risk factors for depression do contact their GP regularly and that GPs have reliable data about many known risk factors in their files. In the Netherlands, therefore, the optimal point of contact for selective prevention of late-life depression would be the GP practice. This is described here because a similar line of reasoning could lead to a very different optimal point of contact for selective prevention in other places in the world.

Engaging older people who are currently not depressed in an intervention is not easy. This partly involves the same reasons why the majority of those with full-blown affective disorders remain untreated. Known factors include a combination of (1) lack of knowledge about affective disorders; (2) lack of trust in mental health intervention; (3) lack of time, trained personnel, and resources; and (4) the stigma that remains attached to mental illness. Besides these factors, barriers to engage people in depression prevention are consonant with the difficulties in engaging people in any type of prevention. The reality of being human may be that we tend to dislike doing things now to avoid harm later.

The interventions that have been designed are mostly light versions of interventions known to be effective in treating depression. This involves light or self-help versions of cognitive therapy, interpersonal therapy, reminiscence, and problem solving. Often these are modified to cater for people exposed to specific risk factors and circumstances (such as having recently lost a partner or living with a chronic

illness). Other ingredients involve engaging in pleasant activities, physical activity, using nutritional supplements such as vitamin D and fish oils, and exposure to bright light.

Indicated Prevention

Indicated prevention engages older people who do have symptoms of depression but who have not (yet) developed a full-blown affective disorder. Given the ongoing discussion as to where exactly the boundary between affective symptoms and disorders should be drawn, drawing a firm line between indicated prevention and treatment is hazardous. However, in a staging model this may not be so problematic. The idea is that any intervention should be proportional and that the aim is to generate health benefit for those involved. Older people with subthreshold or subclinical depressive symptoms are at very high risk to develop full-blown disorders whichever way we define these states (Beekman et al., 2002). Moreover, they do have symptoms and these symptoms interfere with their well-being and daily functioning. These two considerations help to tip proportionality even more toward active intervention. It is therefore no wonder that, when epidemiological data are used to empirically search out which preventative approach may be most fruitful, indicated prevention is a prominent outcome (Schoevers et al., 2006; Smit, Ederveen, Cuijpers, Deeg, & Beekman, 2006). Similarly, these considerations have probably resulted in the fact that the majority of prevention trials conducted so far involve indicated prevention (see earlier discussion).

A drawback of indicated prevention is that participants need to be diagnosed with "symptoms but no disorder." The trials that have been conducted in this area mostly recruited participants through screening. A positive screen on a depression screener implies that some significant symptoms are there. In a next diagnostic step, the outcome may either be that there exists a full-blown affective disorder (in which case the patient is referred for treatment) or that there is no such disorder (in which case the patient is offered the preventative intervention). Considering the staging model (Fig. 25.1), we are now one step further downstream from selective prevention. This means that those eligible for indicated prevention are a subset of those with known risk factors. One may therefore start

identifying those with risk factors (preferably through existing records) and then screen out those with ultra high risk (offering them indicated prevention) or fully developed disorders (offering these people treatment).

The interventions that have been tested are similar to those described for selective prevention. Given the lower numbers involved, the higher a priori risk of disease, and the fact that there are symptoms already, more incisive interventions may be acceptable here. A study in the Netherlands tested a program that was organized along the lines of stepped care. In this program all the older participants with "depressive symptoms but no disorder" were offered a choice of educational and self-help interventions first, slowly stepping up the intensity of the intervention if the symptoms remained present (van 't Veer et al., 2009).

Relapse Prevention

Having been depressed before is one of the most consistent risk factors for depression in the future. This is true at all ages and the risk becomes especially strong if recovery was not complete, involving residual symptoms (Reynolds et al., 2011). In terms of the staging model, we now progress to an area beyond treatment. Given the damage a depressive episode can do and the high risk of recurrence, relapse prevention should be part of any treatment plan of affective disorders. This is especially true in older people, as the risk of relapse appears to rise with age (Hardeveld, Spijker, de Graaf, Nolen, & Beekman, 2010).

Besides the interventions mentioned earlier, here the option of maintenance treatment is, of course, important. However, as was discussed in the introduction, this is beyond the scope of this chapter.

EFFECTIVENESS OF PREVENTION IN LATE-LIFE DEPRESSION

Is there an evidence base with regard to thoroughly tested interventions in the area of preventing late-life depression? If there is, does this provide the necessary data to make evidence-based policy decisions as to where limited funds should be directed? During the past decade a number of well-designed randomized clinical trials have been conducted to test the effects of prevention of depression among older people (Beekman et al.,

2010; Cuijpers & Beekman, 2003).

Universal Prevention

In the area of universal prevention, the aim is to reduce the prevalence of depression in the community. In the area of universal prevention, the aim is to reduce the prevalence of depression in the community. In the area of universal prevention, the aim is to reduce the prevalence of depression in the community.

Selective Prevention

Pitceathly et al. (2006) conducted a controlled trial of selective prevention in late-life depression. The trial was designed to test the effectiveness of a 12-week cognitive behavioral therapy (CBT) program in older people with late-life depression. The trial was designed to test the effectiveness of a 12-week cognitive behavioral therapy (CBT) program in older people with late-life depression. The trial was designed to test the effectiveness of a 12-week cognitive behavioral therapy (CBT) program in older people with late-life depression.

2010; Cuijpers, van Straten, Smit, Mihalopoulos, & Beekman, 2008).

Universal Prevention

In the area of universal prevention, van de Rest et al. (2008) conducted a three-armed randomized controlled trial testing whether low or higher dose supplementation with n-3 polyunsaturated fatty acids (PUFAs) would help to prevent depression among healthy older people in the community. Over 26 weeks, 302 participants were randomized to consume placebo, 400 mg, or 1,800 mg doses of PUFA. Although the plasma concentrations demonstrated high intake fidelity, there were no effects at either the 13-week or 26-week evaluation.

Selective Prevention

Pitceathly et al. (2009) conducted a randomized controlled trial to test whether a brief psychological intervention may help preventing anxiety or depressive disorders among recently diagnosed cancer patients. Although not primarily aimed at older people, this trial is of interest as it targets cancer patients. The trial was large (465 patients were recruited, of whom 313 completed the study), testing (1) whether the brief intervention would be effective and (2) whether the timing of the start of the intervention may make a difference, while (3) stratifying the participating patients with regard to their a priori risk for depression and anxiety. This trial is one of very few studies in which the effect of the level of a priori risk of depression on the effect could be examined. After 12 months there was no overall difference between those exposed to the intervention and the controls. However, among patients at high risk for depression or anxiety the intervention was effective (OR = 0.54, 95% CI 0.29–1.00), while in the low-risk patients there was no difference. All the patients included were at risk for depression due to their recent cancer diagnosis, which means this trial is an example of selective prevention. However, the results of the stratified analyses suggest that there is a gradient of effect in favor of those with the highest a priori risk.

Robinson et al. (2008) tested the effect of escitalopram and problem solving to prevent depression in patients with stroke. The rationale for this study was that more than half of the patients experiencing a stroke develop depression later on. This

is a further example of selective prevention among older people at high risk due to a physical illness. Within 3 months after a stroke, 176 nondepressed patients were randomized to escitalopram, placebo, or problem-solving therapy. Over the 12-month intervention period, the patients receiving placebo were significantly more likely to develop depression than both those receiving escitalopram (HR 4.5; 95% CI 2.4–8.2) and problem-solving therapy (HR 2.2, 95% CI 1.4–3.5).

A further example is the study by Rovner et al. (2007), in which the effect of problem-solving therapy among patients with macular degeneration was tested. The rationale here was that macular degeneration leads to irreversible loss of vision and corresponding disability, which carries a high risk of concomitant depression. In this randomized controlled trial, 206 nondepressed patients with existing macular degeneration in one eye, plus a recent manifestation in the other eye, were randomized to either care as usual or problem-solving therapy (eight weekly sessions). After 8 weeks, the incidence of depressive disorders was lower among those exposed to problem-solving therapy (HR 0.39, 95% CI 0.17–0.92).

Yet another example of selective prevention among older people with chronic disease is a study by de Jonge et al. (2009). They administered a multifaceted nurse-led intervention to prevent major depression in 100 patients with diabetes or rheumatism, who were considered to be medically complex. At 1 year follow-up the incidence of those randomized to the intervention was 36%, as compared to 63% in the usual care group.

Indicated Prevention

Moving on to indicated prevention, van 't Veer et al. (2009) tested the effect of a stepped-care program to prevent depression and anxiety among older GP patients with subthreshold depressive symptoms. In this randomized controlled trial 170 patients with subthreshold symptoms were randomized to either care as usual or a stepped-care prevention program. The steps lasted 3 months each and included (1) watchful waiting, (2) guided self-help, (3) problem solving, and (4) referral to the GP for further evaluation or treatment. Over the year the intervention lasted it was successful in reducing the incidence of DSM anxiety or depressive disorders (HR 0.49; 95% CI 0.24–0.98). A year later these effects had persisted.

Walker et al. (2010) tested the effects of (1) mental health literacy, (2) folic acid and vitamin B12 supplementation, and (3) physical activity against placebo conditions among elderly with elevated distress scores in the community. This was a huge trial (909 older adults randomized) in which a factorial design was used, which allowed the authors to test each intervention against placebo, while also testing for interactions between the interventions. As no diagnostic measures were available, some of the participants may have had full-blown disorders and, moreover, it remains unknown what the effect of the interventions may have been on the incidence of full-blown disorders. The results were that, at 24 months follow-up, none of the interventions had any effect on the level of depressive symptoms. During the 24 months follow-up, the only significant effect that was noted was a small effect ($d = 0.12$) of the health literacy intervention at 6 weeks. Although trends remained after that, they were not significant.

Two recent studies (Konnert, Dobson, & Stelmach, 2009; Pot et al., 2010) tested whether psychological interventions (cognitive-behavioral therapy and life review) were effective to reduce depressive symptoms in those with elevated symptoms but no diagnosis. Both found effects, but it remains unsure whether this had an effect on the incidence of affective disorders.

To summarize, the past decade has seen a series of high-quality preventive trials conducted in the area of late-life depression. The trials published have generally shown effects that are both statistically and clinically relevant, and there are indications that the efficacy and the efficiency of interventions are better when elderly with higher a priori risk of depression are included.

CONCLUSION

Providing adequate care to older people is one of the huge challenges facing society all over the world. Depression is a treatable disorder at any age, and it has enormous impact on well-being, functioning, morbidity, and mortality of older people. Despite this, even in the current time and in the richer parts of the world, only a minority of older people with depression are treated adequately. Being able to prevent depression efficiently with interventions that can be feasibly scaled up to be useful at a community level would constitute a way out of the dilemma that treating all older

patients with depression will remain impossible in the future. The present chapter was written with a developmental framework in mind. Depression is a very heterogeneous disorder with an extremely variable course. This is especially true in later life, where the palette of risk and prognostic factors becomes much more varied than among younger adults. A staging and profiling approach to diagnosis is advocated, thereby drawing attention to the early stages of development of affective disorders. The (as yet untested) premises behind this are that, during the early stages of development, relatively light interventions may be effective in averting the development of full-blown disorders, while these interventions lose their effectiveness later on. Examples of the interventions that have been tested to prevent depression were described, as were their effects. It appears that, indeed, relatively cheap, low-intensity interventions may be effective in the early stages of development of depression among older adults. Although much work remains to be done in this area, it seems that the efficiency and also feasibility of intervention program may be better when targeting groups of elderly at higher a priori risk for depressive disorders. As epidemiological data demonstrating which groups of elderly are at high risk are in place, these could be translated into strategies to effectively identify and engage elders at risk. Trials also show that there are personal, practical, ethical, and economic barriers to engaging large numbers of elderly. Increasing the reach of prevention is probably one of the most important issues at this time. Given known risk factors and strategies to engage older people, designing working prevention programs depends very much on fitting the data with local circumstances. Implementing effective prevention programs that make a lasting, demonstrable, and truly significant difference in the incidence of depression has remained elusive as yet. This probably takes more than a combination of good science and good intentions. However, being able to demonstrate that prevention is feasible and that it works is a necessary first step toward that goal, and we should applaud the work that has gone into coming this far.

Disclosures

Dr Beekman has received unrestricted research grants from Eli Lilly, Astra Zeneca, and Jansen and Shire. He has served on the speakers bureaus for Eli Lilly and Lundbeck.

Dr. Cuipers has nothing to disclose.

Dr. Smit has nothing to disclose.

REFERENCES

- Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). "Vascular depression" hypothesis *Archives of General Psychiatry*, 54(10), 915-922.
- Beekman, A. T. F. (2004). Psychiatrische epidemiologie: van observatie naar experiment. [Psychiatric epidemiology: From observation to experiment]. Inaugural lecture Vrije Universiteit, September 17, 2003. *Maandblad Geestelijke Volksgezondheid*, 59, 587-599.
- Beekman, A. T. F., Geerlings, S. W., Deeg, D. J. H., Smit, J. H., Schoevers, R. S., de Beurs, E., & van Tilburg, W. (2002). The natural history of late-life depression: A 6-year prospective study in the community. *Archives of General Psychiatry*, 59, 605-611.
- Beekman, A. T. F., Smit, F., Stek, M. S., Reynolds, C. F., & Cuijpers, P. (2010). Preventing depression in high risk groups. *Current Opinion in Psychiatry*, 23, 8-11.
- Cuijpers, P. (2003). Examining the effects of prevention programmes on the incidence of new cases of mental disorders: the lack of statistical power. *American Journal of Psychiatry*, 160, 1385-1391.
- Cuijpers, P., van Straten, A., Smit, F., Mihalopoulos, C., & Beekman, A. (2008). Preventing the onset of depressive disorders: A meta-analytic review of psychological interventions. *American Journal of Psychiatry*, 165, 1272-1280.
- De Jonge, P., Hadj, F. B., Boffa, D., Zdrojewski, C., Dorogi, Y., So, A., ... Stiefel, F. (2009). Prevention of major depression in complex medical ill patients: Preliminary results from a randomized controlled trial. *Psychosomatics*, 50, 227-233.
- Dighe, S., Purkayastha, S., Swift, I., Tekkis, P. P., Darzi, A., A'Hern, R., & Brown, G. (2010). Diagnostic precision of CT in local staging of colon cancers: A meta-analysis. *Clinical Radiology*, 65(9), 708-719.
- Fava, G. A., & Kellner, R. (1993). Staging: A neglected dimension in psychiatric classification. *Acta Psychiatrica Scandinavica* 87, 225-230.
- Fukui, S., Ogawa, K., Ohtsuka, M., & Fukui, N. (2008). A randomized study assessing the efficacy of communication skill training on patients' psychologic distress and coping: Nurses' communication with patients just after being diagnosed with cancer. *Cancer*, 113, 1462-1470.
- Hardeveld, F., Spijker, J., de Graaf, R., Nolen, W., & Beekman, A. T. F. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica*, 122, 184-191.
- Hariharan, D., Constantinides, V. A., Froeling, F. E., Tekkis, P. P., & Kocher, H. M. (2010). Ppreoperative staging of pancreatico-biliary cancers—A meta-analysis. *European Journal of Surgical Oncology*, 36(10), 941-948.
- Hetrick, S. E., Parker, A. G., Hickie, I. B., Purcell, R., Yung, A. R., & McGorry, P. D. (2008). Early identification and intervention in depressive disorders: Towards a clinical staging model. *Psychotherapy and Psychosomatics*, 77(5), 263-270.
- Konnert, C., Dobson, K., & Stelmach, L. (2009). The prevention of depression in nursing home residents: A randomized clinical trial of cognitive-behavioral therapy. *Aging and Mental Health*, 13(2), 288-299.
- Lamers, F., de Jonge, P., Nolen, W. A., Smit, J. H., Zitman, F. G., Beekman, A. T. F., & Penninx, B. W. J. H. (2010). Identifying depressive subtypes is a large cohort study: Results from the Netherlands Study of Depression and Anxiety. *Journal of Clinical Psychiatry*, 71, 1582-1589.
- Licht-Strunk, E., van Marwijk, H. W. J., Hoekstra, T., Twisk, J. W. R., de Haan, M., & Beekman, A. T. F. (2009). The prognosis of late life depression in primary care patients. *British Medical Journal*, 338, a3079.
- McGorry, P. D. (2007). Issues for DSM-V: Clinical staging: A heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. *American Journal of Psychiatry*, 164, 859-860.
- Mrazek, P. J., & Haggerty, R. J. (Eds.). (1994). *Reducing risks for mental disorders*. Washington, DC: National Academic Press.
- Paesmans, M., Berghmans, T., Dusart, M., Garcia, C., Hossein-Foucher, C., Lafitte, J. J., ... European Lung Cancer Working Party. (2010). Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: Update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. *Journal of Thoracic Oncology*, 5(5), 612-619.
- Pitceathly, C., Maguire, P., Fletcher, I., Parle, M., Tomenson, B., & Creed, F. (2009). Can a brief psychological intervention prevent anxiety or depressive disorders in cancer patients? A randomised controlled trial. *Annals of Oncology*, 20, 928-934.
- Pot, A. M., Bohlmeijer, E. T., Onrust, S., Melenhorst, A. S., Veerbeek, M., & De Vries, W. (2010). The impact of life review on depression in older adults: a randomized controlled trial. *International Psychogeriatrics*, 22(4), 572-81.

- Reynolds, C. F., III, Butters, M. A., Lopez, O., Pollock, B. G., Dew, M. A., Mulsant, B. H., ... DeKosky, S. T. (2011). Maintenance treatment of depression in old age: A randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Archives of General Psychiatry*, 68(1), 51–60.
- Riemersma-van der Lek, R. F., Swaab, D. F., Twisk, J., Hol, E. M., Hoogendijk, W. J., & Van Someren, E. J. (2008). Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: A randomized controlled trial. *Journal of the American Medical Association*, 299, 2642–2655.
- Robinson, R. G., Jorge, R. E., Moser, D. J., Acion, L., Solodkin, A., Small, S. L., ... Arndt, S. (2008). Escitalopram and problem solving therapy for prevention of post stroke depression: A randomised controlled trial. *Journal of the American Medical Association*, 299, 2391–2400.
- Rovner, B. W., Casten, R. J., Hegel, M. T., Leiby, B. E., & Tasman, W. S. (2007). Preventing depression in age-related macular degeneration. *Archives of General Psychiatry*, 64, 886–892.
- Schoevers, R. A., Smit, F., Deeg, D. J. H., Cuijpers, P., Dekker, J., van Tilburg, W., & Beekman, A. T. (2006). Do we know where to start? Prevention of late-life depression in primary care. *American Journal of Psychiatry*, 163, 1611–1621.
- Smit, F., Ederveen, A., Cuijpers, P., Deeg, D., & Beekman, A. (2006). Opportunities for cost-effective prevention of late-life depression: An epidemiological approach. *Archives of General Psychiatry*, 63, 290–296.
- Spijker, J., de Graaf, R., Bijl, R. V., Beekman, A. T., Ormel, J., & Nolen, W. A. (2003). Duration of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *British Journal of Psychiatry*, 181, 208–213.
- Sun, X., Steffens, D. C., Au, R., Folstein, M., Summergrad, P., Yee, J., ... Qiu, W. Q. (2008). Amyloid-associated depression: a prodromal depression of Alzheimer disease? *Archives of General Psychiatry*, 65(5), 542–550.
- van de Rest, O., Geleijnse, J. M., Kok, F. J., van Staveren, W. A., Hoefnagels, W. H., ... de Groot, L. C. (2008). Effect of fish oil supplementation on mental well-being in older subjects: a randomised, double-blind, placebo-controlled trial. *American Journal of Clinical Nutrition*, 88, 706–713.
- van 't Veer, P. J., van Marwijk, H. W. J., Smit, F., van Hout, H. P., van der Horst, H. E., Cuijpers, P., ... Beekman, A. T. (2009). Stepped care prevention of anxiety and depression in late life: A randomised controlled trial. *Archives of General Psychiatry*, 66, 297–304.
- Vogelzangs, N., Beekman, A. T., Boelhouwer, I. G., Bandinelli, S., Milanese, Y., Ferrucci, L., & Penninx, B. W. (2011). Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. *Journal of Clinical Psychiatry*, 72, 598–604.
- Walker, J. G., Mackinnon, A. J., Batterham, P., Jorm, A. F., Hickie, L., McCarthy, A., ... Christensen, H. (2010). Mental health literacy, folic acid and vitamin B12, and physical activity for the prevention of depression in older adults: Randomised controlled trial. *British Journal of Psychiatry*, 197(1), 45–54.
- Xing, Y., Bronstein, Y., Ross, M. I., Askew, R. L., Lee, J. E., Gershenwald, J. E., ... Cormier, J. N. (2011). Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: A meta-analysis. *Journal of the National Cancer Institute*, 103(2), 129–42.